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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/700,712	11/13/2001	Nils Carlin	REF/CARLIN/509	7758

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EXAMINER

DEVI, SARVAMANGALA J N

ART UNIT

PAPER NUMBER

1645

DATE MAILED: 09/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/700,712

Applicant(s)

CARLIN ET AL.

Examiner

S. Devi, Ph.D.

Art Unit

1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 June 2006.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 17-29 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 17-29 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 24 January 2005 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

REQUEST FOR CONTINUED EXAMINATION

1) A request for continued examination under 37 C.F.R. 1.114, including the fee set forth in 37 C.F.R. 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R. 1.114, and the fee set forth in 37 C.F.R. 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 C.F.R. 1.114. Applicants' submission filed on 01/03/06 has been entered.

Applicants' Amendments

2) Acknowledgment is made of Applicants' amendments filed 06/21/06 and 01/03/06 in response to the final Office Action mailed 07/01/05. The amendment filed 06/21/06 is compliant.

Status of Claims

3) New claims 24-29 have been added via the amendment filed 01/03/06.
Claims 17, 18, 21 and 23 have been amended via the amendment filed 01/03/06.
Claims 17-29 are pending and are under examination.

Prior Citation of Title 35 Sections

4) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

5) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Objection(s) Withdrawn

6) The objection to claim 18 made in paragraph 20(a) of the Office Action mailed 07/01/05 withdrawn in light of Applicants' amendment to the claim.

Objection(s) Maintained

7) The objection to claim 23 made in paragraph 20(b) of the Office Action mailed 07/01/05 is maintained for reasons set forth therein.

Rejection(s) Withdrawn

8) The rejection of claim 17 made in paragraph 17(a) of the Office Action mailed 07/01/05

under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

9) The rejection of claim 18 made in paragraph 17(b) of the Office Action mailed 07/01/05 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

10) The rejection of claim 21 made in paragraph 17(c) of the Office Action mailed 07/01/05 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

11) The rejection of claim 23 made in paragraph 17(d) of the Office Action mailed 07/01/05 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

12) The rejection of claim 23 made in paragraph 17(e) of the Office Action mailed 07/01/05 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

13) The rejection of claims 19-23 made in paragraph 17(f) of the Office Action mailed 07/01/05 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the base claim.

14) The rejection of claims 17-21 and 23 made in paragraph 18 of the Office Action mailed 07/01/05 under 35 U.S.C. § 102(b) as being anticipated by Morona *et al.* (EP 0,251,579 – Applicants' IDS), is withdrawn in light of Applicants' amendment to the claims and/or the base claim.

15) The rejection of claim 22 made in paragraph 19 of the Office Action mailed 07/01/05 under 35 U.S.C. § 103(a) as being unpatentable over Morona *et al.* (EP 0,251,579 – Applicants' IDS) in view of Arntzen *et al.* (US 6,194,560, already of record), is withdrawn in light of Applicants' amendment to the base claim.

Rejection(s) under 35 U.S.C. § 112, First Paragraph (New Matter)

16) Claim 17, and claims 19-23 and 26-29 that depend therefrom, are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the

time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 17, as amended, includes the new limitation: *thyA* strain of *Vibrio cholerae* deprived of its *thyA* gene 'functionality by selected nucleotide sequence deletion and/or insertion' in the chromosome. Applicants do not point to a specific part(s) of the specification that provides descriptive support for the new limitations. A review of the specification indicates that page 9 of the specification describes *thyA* mutants of *V. cholerae* obtained by complete deletion of the *thyA* gene from the chromosome, or by partial deletion of the *thyA* gene and the Kan^R gene block. The instant specification does not support description of a *thyA* strain of *V. cholerae* as claimed currently wherein the strain is deprived of its *thyA* gene functionality 'by selected nucleotide sequence deletion and/or insertion' anywhere in its chromosome. Therefore, the above-identified limitations in the instant claim are considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are respectfully requested to point to the descriptive support for the above-identified limitation(s) by identifying the specific lines and pages in the specification as filed, or to remove the new matter from the claim(s).

17) Claim 24 is rejected under 35 U.S.C § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

New claim 24 includes the limitations: 'D*thyA* strain of *Vibrio cholerae* wherein the structural *thyA* gene of the chromosome has the nucleotide sequence of nucleotides 738-1688 in the SEQ ID NO: 1 before it has been deprived of its functionality as a *thy A* gene and wherein approximately 200 base pairs of said structural *thy A* gene is deleted followed by an insert of a non-coding region of DNA'. Applicants point to lines 18-24 of page 6 of the specification, and state that this part of the specification provides the basis for the new claim 24. However, this part of the specification does not describe a 'D*thyA* strain of *Vibrio cholerae*', does not mention of a 'structural *thyA* gene of the chromosome having the nucleotide sequence of nucleotides 738-

1688 in the SEQ ID NO: 1' and of the deletion of 'approximately' 200 base pairs of 'said structural *thyA* gene is deleted followed by an insert of a non-coding region of DNA'.

Therefore, the above-identified limitations in the instant claims are considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are respectfully requested to point to the descriptive support for the above-identified limitation(s) by identifying the specific lines and pages in the specification as filed, or to remove the new matter from the claim(s).

18) Claims 25, 26 and those dependent therefrom are rejected under 35 U.S.C § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

New claims 25 and 26 include the limitations: 'the strain has its structural *thyA* gene removed from the *thyA* gene of the chromosome'. Applicants point to lines 25-29 of page 6 and the experimental part of the specification and state that these parts of the specification provide the basis for the new claims 25 and 26. However, these parts of the specification do not describe what appears to be a narrower structural *thyA* gene removed from a broader '*thyA* gene of the chromosome'. Therefore, the above-identified limitations in the instant claims are considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are respectfully requested to point to the descriptive support for the above-identified limitation(s) by identifying the specific lines and pages in the specification as filed, or to remove the new matter from the claim(s).

Rejection(s) under 35 U.S.C. § 112, First Paragraph

19) Claims 17-29 are rejected under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure, because

the specification does not provide evidence that the claimed biological material is (1) known and readily available to the public; (2) reproducible from the written description, e.g. sequenced; or (3) deposited.

Instant claims are directed to a $\Delta thyA$ strain of *Vibrio cholerae* deprived of its *thyA* gene functionality by deletion or insertion of nucleotides at the *thyA* gene locus as recited. It is recited to have approximately 200 unspecified base pairs from nucleotides 738-1688 in the SEQ ID NO: 1 deleted followed by an insert of a non-coding region of DNA. How many base pairs equate to 'approximately 200' base pairs and which exact approximately 200 base pairs from within 738-1688 nucleotides in SEQ ID NO: 1 are deleted are not specifically described. It is apparent that the claimed $\Delta thyA$ strain of *Vibrio cholerae* having this deletion is an element required to practice the invention. The specification describes a single $\Delta thyA$ strain of *Vibrio cholerae*, JS1569 $\Delta thyA$. See line 29 of page 6; and line 4 of page 7 of the specification. As a required element, the specifically recited strain(s) must be known and readily available to the public, or obtainable by a reproducible method set forth in the specification. If not so obtainable or available, the enablement requirements of 35 U.S.C. § 112, first paragraph, may be satisfied by a deposit of the recited strains at an acceptable depository. From the instant specification, it appears that the strain has not been deposited at an accepted depository under the provisions of the Budapest Treaty. If such a deposit has already been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by Applicants or assignees, or a statement by an attorney of record who has a registration number and has authority and control over the conditions of deposit over his or her signature, is required. The statement should state that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that **all** restrictions upon public access to the deposit will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced, if viable samples cannot be dispensed by the depository. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each state. The statement should identify the deposited strain(s) by its depository accession number, establish that the deposited strain(s) is the same as the one described in the specification/claims, and establish that the deposited strain(s) was in Applicants' possession at the time of filing. As a means of satisfying the necessary criteria of the deposit

rules and to show that each claimed bacterial strain(s) is the same as the one deposited, Applicants may submit a copy of the contract or a notice of acceptance of the strain(s) by the depository.

Applicants' attention is directed to *In re Lundack*, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 C.F.R § 1.801-1.809 for further information concerning deposit practice.

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

20) Claims 17-29 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) New claim 24 is vague, indefinite and confusing in the limitation: 'DthyA strain ... according to claim 18', because claim 18 is not drawn to a 'DthyA strain'. What exactly does 'DthyA' stand for is not clear.

(b) New claim 24 has improper antecedent basis in the limitation: 'the structural *thyA* gene of the chromosome'. Claim 24 depends from claim 18, which does not recite any 'structural *thyA* gene of the chromosome'.

(c) New claim 25 is indefinite and confusing in the limitation: 'the strain has its structural *thyA* gene removed from the *thyA* gene of the chromosome', because it is unclear how the structural *thyA* gene differs in scope from 'the *thyA* gene of the chromosome'. Are these two different *thyA* genes of the same strain? Does the chromosome of *Vibrio cholerae* contain two *thyA* genes, i.e., a structural *thyA* gene comprised within the *thyA* gene? Clarification/correction is requested.

(d) Analogous criticism applies to the new claim 26.

(e) New claim 24 is vague, indefinite and confusing in the limitations: 'DthyA strain of *Vibrio cholerae*', 'approximately' 200 base pairs, and 'insert of a non-coding region of DNA', because it is unclear what is encompassed in these limitations. Is the recited DNA non-coding region of homologous or heterologous origin?

(f) Claim 17 is vague, indefinite, confusing and has incorrect antecedence in the recitation: 'the at least one episomal autonomously replicating DNA elements further comprises' (see lines 5 and 6) [Emphasis added]. The earlier part of the claim includes the recitation: 'at least one episomal autonomously replicating DNA element' (see lines 3 and 4). For proper

antecedence, it is suggested that Applicants replace the phrase with: --the at least one episomal autonomously replicating DNA element further comprises--.

(g) Claim 18 is incorrect and inconsistent with claims 17 and 19-20 in the limitation 'cholerae'. To be consistent with the limitation in claims 17 and 19-20 and to be consistent with the practice used in the art, it is suggested that Applicants italicize the limitation.

(h) Claim 20 is incorrect and indefinite in the limitation: 'the at least **on** episomal autonomously replicating DNA have element has' [Emphasis added]. The phrase makes no sense.

(i) Claim 24 is confusing in the inconsistent limitations: '*thyA* gene' and '*thy A* gene'.

(j) Claims 19-29, which depend directly or indirectly from claim 17 or claim 18, are also rejected as being indefinite, because of the indefiniteness identified above in the base claim.

Rejection(s) under 35 U.S.C. § 102

21) Claims 17-19 are rejected under 35 U.S.C. § 102(b) as being anticipated by Valle *et al.* (*Infect. Immun.* 68: 6411-6418, 01 November 2000).

The instant claims are granted priority to the instant application due to the new matter identified above, and therefore, the reference of Valle *et al.* qualifies as prior art.

Valle *et al.* taught a live, attenuated, non-proliferative *thyA*-defined mutant (Δ *thyA*) of *Vibrio cholerae* strain which was constructed after cloning and nucleotide sequencing the *thyA* gene of *Vibrio cholerae*. This genetically defined stable mutant strain of *Vibrio cholerae*, 638T, is generated by allelic replacement of the *thyA* gene in the chromosome of the vaccine candidate strain 638 by a 300 bp-deletion from its *thyA* gene. The 638T strain containing or complemented with the pVT1 plasmid (i.e., autonomously replicating DNA element) carrying a functional *thyA* gene is taught, wherein the plasmid enables the strain to grow in the absence of thymine in a growth medium such as LB medium. The mutant strain was able to colonize the small bowel of mice in the infant mouse cholera model to the same extent as its parenteral strain 638 and evoked a strong immune response in rabbits after intraduodenal administration. See abstract; pages 6411, 6412, 6414 and 6417.

Claims 17-19 are anticipated by Valle *et al.*

Rejection(s) under 35 U.S.C. § 103

22) Claim 22 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Valle *et al.* (*Infect. Immun.* 68: 6411-6418, 01 November 2000) in view of Arntzen *et al.* (US 6,194,560, already of record).

The reference of Arntzen *et al.* is applied in this rejection because it qualifies as prior art under subsection (e) of 35 U.S.C. § 102 and accordingly is not disqualified under U.S.C. 103(a).

The teachings of Valle *et al.* have been explained above which do not disclose that their mutant *Vibrio cholerae* encodes *E. coli* LTB. However, Valle *et al.* expressly taught that the introduction of a stable and defined thymidine auxotrophy in *Vibrio cholerae* provides an useful tool for the expression of foreign genes in the vaccine strain from a balanced lethal system that would ensure the production of desired gene products during colonization of the human intestine. See page 6417.

However, fusion of the *E. coli* LTB to a nucleotide sequence encoding an antigen in a recombinant bacterial strain and co-expression of the antigen along with LTB was well known in the art at the time of the invention. For instance, Arntzen *et al.* taught the routine and conventional fusion of *E. coli* LTB to sequences that encode other antigens for co-expression of both, since LTB has the advantageous property of serving both as an antigen and as an adjuvant (see first full paragraph in column 14; and lines 37-41 in column 15).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention as made to fuse Arntzen's *E. coli* LTB gene into the plasmid element of Valle's mutant *Vibrio cholerae* strain to produce the instant invention with a reasonable expectation of success. One of skill in the art would have been motivated to produce the instant invention for the expected benefit of advantageously co-expressing a foreign *E. coli* LTB gene via Valle's mutant *Vibrio cholerae* strain during colonization as taught by Valle *et al.*

Claim 22 is *prima facie* obvious over the prior art of record.

Remarks

23) Claims 17-29 stand rejected.

24) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Central Fax number, (571) 273-8300, which receives transmissions 24 hours a day and 7 days a week.

25) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.Mov>. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

26) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's Acting Supervisor, Albert Navarro, can be reached on (571) 272-0861.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

September, 2006


S. DEVI, PH.D.
PRIMARY EXAMINER